Response to Comments Pertaining to the Notice of Intent to List Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA as Causing Reproductive Toxicity under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
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On February 7, 2014, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List[1] atrazine, propazine, simazine, DACT (G-28273; 2,3-diamino-6-chloro-*s*-triazine), DEA (G-30033; des-ethyl atrazine) and DIA (G-28279; des-isopropyl atrazine), hereafter referred to collectively as triazines, under Proposition 65[2] as chemicals known to the State to cause reproductive toxicity (developmental and female reproductive endpoints). The action was based on Proposition 65 statutory requirements[3] and on the authoritative bodies provision[4] of the Proposition 65 implementing regulations. OEHHA found that these triazines meet the critieria for listing via this mechanism based on:

- Conclusions by the US Environmental Protection Agency (US EPA) in several documents that these triazines cause developmental and reproductive effects (US EPA 2002b; 2005; 2006a,b,c,d)[5].

[1] Notice of Intent to List: Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilpkg41Triazines.html

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.) hereinafter referred to as Proposition 65 or the Act.

[3] Health and Safety Code section 25249.8(b)

[4] Title 27, Cal. Code of Regulations, section 25306.

[5] US EPA (2002b). Office of Pesticide Programs. Special Docket for Pesticide Reregistration Risk Assessments. Memorandum on ATRAZINE/DACT - Fourth Report of the Hazard Identification Assessment Review Committee. TXR NO. 0050592

US EPA (2005). Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED) which includes a New Use on Grain Sorghum. PC Code: 080808, DP Barcode: D323271 Memorandum from J. Morales et al. Office of Pesticide Programs and Toxic Substances (OPPTS) Health Effects Division to D. Sherman OPPTS, December 13, 2005.

US EPA (2006a). Decision Documents for Atrazine. US EPA OPPTS. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf

US EPA (2006b). Triazine Cumulative Risk Assessment (March 28, 2006). Available at http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#triazine

US EPA (2006c). Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Progress and Risk Management Decision (TRED) for Propazine. US EPA OPPTS , EPA 738-R-06-009 Available at http://www.epa.gov/opp00001/reregistration/status_page_p.htm

US EPA (2006d). Reregistration Eligibility Decision Document for Simazine. US EPA OPPTS. EPA 738-R-06-008. Available at http://www.epa.gov/opp00001/reregistration/status_page_s.htm

- US EPA's adoption of reference doses based on female reproductive and developmental endpoints. (US EPA 2002b; 2006a,b,c,d)
- The scientific evidence relied upon by US EPA[6].

This document responds to public comments received on the Notice of Intent to List these six triazines under Proposition 65.

Under Section 25306, a chemical is identified as causing reproductive toxicity, including developmental toxicity, if it has been "formally identified" by an authoritative body as causing reproductive toxicity. A chemical has been "formally identified" pursuant to section 25306 if it has been included in a list of chemicals causing reproductive toxicity published by the authoritative body; is the subject of a report which is published by the authoritative body and which concludes that the chemical causes reproductive toxicity; or has been "otherwise identified" as causing reproductive toxicity by the authoritative body in a document that indicates that the identification is a final action, and if the list, report, or document meets specified criteria in section 25306(d)(2). US EPA is designated as an authoritative body for purposes of listing chemicals as causing reproductive toxicity pursuant to Section 25306.

OEHHA has reviewed the conclusions and statements in US EPA documents from 2002, 2005 and 2006 and determined that these conclusions and statements satisfy the Section 25306(d)(1) requirement that the triazines are the subject of reports published by the authoritative body that conclude that the triazines cause reproductive toxicity, and that the documents meet the section 25306(d)(2) criteria, thus satisfying the formal identification criteria in the Proposition 65 regulations. US EPA's conclusions in these documents on which OEHHA relies include the following:

- Reproductive and Developmental Toxicity: In its "Decision Documents for Atrazine", US EPA (2006a) states: "EPA has determined that the triazine pesticides (with a common mechanism group of atrazine, propazine, simazine and their chlorometabolites) have common [*sic*] mechanism of suppression of LH surge and consequent developmental and reproductive effects." (p. 17)

[6] All further references are to sections of Title 27, California Code of Regulations unless indicated otherwise.[7] US EPA indicates that the triazines diminish hypothalamic GnRh, which controls lutenizing hormone, and increase dopamine levels, which diminish prolactin. Changes in levels of hormones such as luteinizing hormone and prolactin are identified by US EPA as "Female Specific Endpoints of Reproductive Toxicity". US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996). Federal Register 61(212):56274-56322 (page 38). Available at http://www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm

- Reproductive and Developmental Toxicity: In its document "Triazine Cumulative Risk Assessment", US EPA (2006b) states:
    - "Atrazine, Simazine, Propazine, and the metabolites Desethyl-s-atrazine (DEA), Desisopropyl-s-atrazine (DIA), and Diaminochlorotriazine (DACT) may be grouped together based on a common end-point (neuroendocrine and neuroendocrine-related developmental, reproductive and carcinogenic effects) and a known mechanism of toxicity for this endpoint." (p. 11)

    - "The underlying mechanism of the endocrine-related changes associated with atrazine and similar triazines is understood to involve a disruption of the hypothalamic-pituitary-gonadal (HPG) axis… In particular, the triazine-mediated changes in the HPG relating to neuroendocrine and neuroendocrine-related developmental and reproductive toxicity *are considered relevant to humans*, and these adverse effects were identified as endpoints for the exposure scenarios selected for consideration in the quantitative cumulative assessment." (p. 4, emphasis added)

    - "Neuroendocrine effects are considered the critical endpoints for assessing the health effects of the CMG [common mechanism group] Triazines. The CMG triazines have been shown to lead to various endocrine-related changes as a result of an effect on the hypothalamic-pituitary-gonadal axis. The consequences of this action include a diminishment of hypothalamic gonadotrophin releasing hormone (GnRH) and norepinephrine levels. These triazines also increase dopamine level which can result in a diminished pituitary secretion of PRL [prolactin]. Therefore, the CMG triazines operate at the level of the hypothalamus. *In both humans and rats*, hypothalamic GnRH controls pituitary hormone secretion (e.g., luteinizing hormone and PRL)[7]. The hypothalamic-pituitary axis is involved in the development of the reproductive system, and its maintenance and functioning in adulthood. Additionally, reproductive hormones modulate the function of numerous other metabolic processes (i.e., bone formation, and immune, central nervous system, and cardiovascular functions). Therefore, altered hypothalamic-pituitary function can potentially broadly affect an individual's functional

[7] US EPA indicates that the triazines diminish hypothalamic GnRh, which controls lutenizing hormone, and increase dopamine levels, which diminish prolactin. Changes in levels of hormones such as luteinizing hormone and prolactin are identified by US EPA as "Female Specific Endpoints of Reproductive Toxicity". US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996). Federal Register 61(212):56274-56322 (page 38). Available at http://www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm

status and lead to a variety of health consequences." (p. 22, emphasis added)

- Reproductive and Developmental Toxicity: In its document "Propazine: Revised HED Risk Assessment for the Tolerance Reassessment Eligibility Decision (TRED)", US EPA (2005) states that propazine and atrazine's mechanism of toxicity "involves a central nervous system (CNS) toxicity, specifically, neurotransmitter and neuropeptide alterations at the level of the hypothalamus, which cause cascading changes to hormone levels, e.g., suppression of the luteinizing hormone surge prior to ovulation resulting in prolonged estrus in adult female rats (demonstrated with atrazine and propazine), and developmental delays, i.e., delayed vaginal opening and preputial separation in developing rats (studied in atrazine and propazine). These neuroendocrine effects are considered the primary toxicological effects of regulatory concern." (p. 17)

The above conclusions satisfy the criterion for formal identification that "the chemical is the subject of a report which is published by the authoritative body and which concludes that the chemical causes … reproductive toxicity".[8] In addition, OEHHA has determined, based on the US EPA documents identified below, that the triazines have been "otherwise identified as causing reproductive toxicity[9]." The basis for this determination is that US EPA has used specific developmental and female reproductive toxicity endpoints as the basis for setting regulatory reference doses (RfDs)[10] for the triazines. The statements that identify these relevant developmental and female reproductive endpoints and provide the basis for OEHHA's determination that US EPA has "otherwise identified" the triazines as reproductive and developmental toxicants include:

- In its "Interim Reregistration Eligibility Decision for Atrazine", US EPA (2006a) states that:
    - Developmental Toxicity: "Delayed ossification of certain cranial bones in fetuses" was the basis of the acute dietary reference dose (RfD) for atrazine and its chlorinated metabolites. (p. 19)

[8] Section 25306(d)(1).
[9] Section 25306(d)(1). "the chemical has otherwise been identified as causing … reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action".
[10] Reference doses are standards established by US EPA to protect human health. For example, the US EPA Guidelines for Developmental Toxicity Risk Assessment (1991). Federal Register 56(234):63798-63826 specify "The $RfD_{DT\ [Developmental\ Toxicity]}$ … is an estimate of a daily exposure to the human population that is assumed to be without appreciable risk of deleterious developmental effects" (page 42). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162#Download

- Female Reproductive Toxicity: Attenuation of pre-ovulatory LH surge was the basis for the chronic RfD. (p. 19)

- Developmental Toxicity: In its Memorandum on ATRAZINE/DACT - Fourth Report of the Hazard Identification Assessment Review Committee, US EPA (2002b) states that: “Delayed or lack of ossification of several sites” in a developmental toxicity study in rats was the basis of the acute dietary reference dose (RfD) for atrazine and DACT. (p. 41)

- In its “Reregistration Eligibility Decision Document for Simazine”, US EPA (2006d) states that:

  - Developmental Toxicity: Increased incidence of fetal “unossified teeth, head, centra vertebrae, sternabrae, and also on rudimentary ribs” was the basis for simazine’s acute RfD for *females ages 13-49*. (p. 16, emphasis added)

  - Female Reproductive Toxicity: Estrous cycle alterations and LH surge suppression was the basis for RfDs for chronic dietary, incidental oral intermediate-term, and dermal and inhalation intermediate and long-term exposures. (pp. 16-17)

- Developmental Toxicity: In its “Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Eligibility Decision (TRED) for Propazine”, in the section titled “Aggregate Risk Assessment”, US EPA (2006c) states: “In a sub-chronic developmental study, incomplete or absent bone formation or ossification was observed in fetal rats following exposure of pregnant rats to propazine. These developmental effects are presumed to occur after a single exposure and are therefore appropriate for consideration in the acute exposure scenario for dietary risk from food. These adverse effects were the basis for identification of a developmental endpoint [for the RfD] for acute dietary exposure to propazine *in females ages 13 to 49*.” (p. 3, emphasis added)

- Female Reproductive Toxicity: In its “Triazine Cumulative Risk Assessment”, in the section titled “Critical Toxicological Effects Of CMG [common mechanism group] Triazines”, US EPA (2006b) states that the selected endpoints for cumulative risk assessment (i.e., RfD development) for the CMG triazines for dietary (drinking water) 90-day exposure scenarios were based on LH surge suppression and estrous cycle alterations. (p. 23)

As a basis for its conclusions about the reproductive and developmental toxicity of the traizines, and its identification of female reproductive and developmental endpoints on which to set RfDs for the triazines, US EPA in its several review documents (US EPA 2002a,b; 2005; 2006a,b,c,d) cited a large number of studies investigating the adverse reproductive and developmental effects of the identified triazines, and the mechanisms of action by which these effects were induced. The studies are identified in Table 1.

Table 1. Studies Cited by US EPA Supporting Formal Identification of the Triazines as Causing Reproductive Toxicity.

Study Cited by US EPA	US EPA MRID Number
Arthur, A. (1984). Segment II Teratology Study in Rabbits: Toxicology/pathology report No. 68-84. Ciba-Geigy Ltd	00143006
Infurna, R. (1984). A Teratology Study of Atrazine Technical in Charles River Rats: Toxicology/Pathology Report No. 60-84. Unpublished study prepared by Ciba-Geigy Corp.	00143008
Salamon, C. (1885). Teratology Study in Albino Rats with Technical Propazine. Report No. 450-1788. Unpublish Study. American Biogenetics Corp.	00150242
Ciba-Geigy Corporation. (1984). Developmental Toxicity (Teratogenicity) Rabbit.	00161407
Epstein, D.; Hazelette, J.; Yau, E. (1991). Two-Generation Reproductive Toxicology Study in Rats: Lab Project Number: 882095. Unpublished study prepared by Ciba-Geigy Corp.	4180360
Mainiero, J.; Youreneff, M.; Giknis, M.; et al. (1987). Two-generation Reproduction Study in Rats: Atrazine Technical: Laboratory Study No. 852063. Unpublished study prepared by Ciba-Geigy Corp.	40431303
Arthur, A. (1984). A Supplement to a Teratology Study of Atrazine Technical in New Zealand White Rabbits. Unpublished study prepared by Ciba-Geigy Corporation.	4056630
Infurna, R. (1984). A Supplement to a Teratology Study of Atrazine Technical in Charles River Rats. Unpublished study prepared by Ciba-Geigy Corporation	40566302
Brown, R.; Lail, L. (1988). Technical Atrazine: Product Chemistry: Laboratory Project ID PC-87-023. Unpublished study prepared by Ciba-Geigy Corporation	40566501
Infurna, R. (1986). A Teratology Study in Rats: Simazine Technical: Study No. 83058; 822099. Unpublished study prepared by CibaGeigy Corp.	40614403

Giknis, M. (1989). A Teratology (Segment II) Study in Rats: Atrazine Technical: Laboratory Study No. 882049. Unpublished study prepared by Ciba-Geigy Corp	41065201
Giknis, M. (1989). A Teratology (Segment II) Study in Rats: Hydroxy-atrazine Technical: Laboratory Study No.872202. Unpublished study prepared by Ciba-Geigy Corp.	41065202
Hummel, H.; Youreneff, M.; Giknis; et al. (1989). Diaminochloro-triazine: A Teratology (Segment II) Study in Rats: Lab Project Number: 872177. Unpublished study prepared by Ciba-Geigy Corp.	41392402
Thakur, A. (1991). Determination of Hormone Levels in Sprague-Dawley Rats Treated with Atrazine Technical: Final Report: Lab Project Number: 483-278. Unpublished study prepared by Hazleton Washington, Inc.	42085001
Thakur, A. (1991). Determination of Hormone Levels in Fischer-344 Rats Treated with Atrazine Technical: Final report: Lab Project Number: 483-279. Unpublished study prepared by Hazleton Washington, Inc.	42146101
Eldridge, J., Wetzel, L., Tisdel, M., and Luempert, L.G. (1993). Determination of Hormone Levels in Sprague-Dawley Rats Treated with Atrazine Technical: Revised Supplement to Final Report. Hazleton Washington, Inc. Lab Project Number: 483-278.	42743902
Eldridge, J.; Wetzel, L.; Tisdel, M. et al. (1993). Determination of Hormone Levels in Fischer-344 Rats Treated with Atrazine Technical: Revised Supplement to Final Report: Lab Project Number: 483-279. Unpublished study prepared by Bowman Gray School of Medicine	42743903
Thompson, S.; Batastini, G.; Arthur, A. (1992). G-28279 Technical: 90-Day Oral Toxicity Study in Dogs: 13-Week Feeding Study in Dogs: Lab Project Number: 912021. Unpublished study prepared by Research Dept. Ciba-Geigy Corp.	43013203
Schneider, M. (1992). G-28279 Technical: 90-Day Oral Toxicity Study in Rats: 3-Month Oral Toxicity Study in Rats (Administration in Food): Lab Project Number: 901261. Unpublished study prepared by Ciba-Geigy Ltd.	43013205
Pettersen, J.; Richter, A.; Gilles, P. (1991). Diaminochlorotriazine (G-28273): 90-Day Oral Toxicity Study in Rats: Lab Project Number: F-00006. Unpublished study prepared by Ciba-Geigy Corp.	43013207
Marty, J. (1992). G-28273 Technical: Teratology Study in Rats: Developmental Toxicity (Teratogenicity) Study in Rats with G-28279 Technical (Oral Administration): Lab Project Number: 901262. Unpublished study prepared by Ciba-Geigy Ltd.	43013208

Tennant, M.; Hill, D.; Eldridge, J.; et al. (1994). Possible antiestrogenic properties of chloro-s-triazines in rat uterus. *J Toxicol Environ Health* **43**: 183-196.	43598617
Tennant, M.; Hill, D.; Eldridge, J.; et al. (1994). Chloro-s-triazine antagonism of estrogen action: Limited interaction with estrogen receptor binding. *J Toxicol Environ Health* **43**:197-211.	43598618
Safe, S.; Chen, I.; Liu, H.; et al. (1995). Failure of Atrazine and Simazine to Induce Estrogenic Responses in MCF-7 Human Breast Cancer Cells. Unpublished study prepared by Texas A&M Univ.; and Univ. of Western Ontario.	43598619
McConnell, R. (1995). A Histomorphologic Reevaluation of the Ovaries, Uterus, Vagina, Mammary Gland, and Pituitary Gland From Sprague-Dawley and Fischer- 344 Female Rats Treated With Atrazine: Lab Project Numbers: 483-278: 483-279. Unpublished study prepared by Ciba-Geigy Corp.	43598622
Safe, S. (1995). Failure of chloro-s-triazine derived compounds to induce estrogenic responses in vivo and in vitro. in Fundamental Applied Toxicology (in Press)	43934403
Morseth, S. (1996). Evaluation of the Luteinizing Hormone (LH) in Female Sprague-Dawley Rats--Pilot Study: Final Report: Lab Project Number: CHV 2386-109: 6791. Unpublished study prepared by Corning Hazleton Inc. (CHV).	43934404
Morseth, S. (1996). Evaluation of the Luteinizing Hormone (LH) in Female Sprague-Dawley Rats--Method Validation: Final Report: Lab Project Number: CHV 2386-110: 6791F: 2386-110. Unpublished study prepared by Corning Hazleton Inc. (CHV).	43934405
Morseth, S. (1996). Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats: Interim Report: Lab Project Number: CHV 2386-111: 6791E: 2386-111. Unpublished study prepared by Corning Hazleton Inc. (CHV).	43934406
Morseth, S (1996). Evaluation of the Luteinizing Hormone (LH) Surge in Atrazine-Exposed Female Sprague-Dawley Rats - (Final) 6-month Interim Report: Lab Project Number: CHV 2386-111:2386-111:6791E. Unpublished Study prepared by Corning Hazelton Inc.	44152102
Lui, C.; Thakur, A. (1999). Statistical Report for Survival and Mammary Tumor Analysis from the Fischer 344/Lati Rat Study (Pinter et al., 1990): Lab Project Number: 6117-998: 1109-99. Unpublished study prepared by Covance Laboratories, Inc.	44917701
Minnema, D.J. (2000). Comparison of the LH surge in female rats administered atrazine, simazine or DACT via oral gavage for one	45058701

month. Covance # 6117-398 Novartis # 1198-98. Covance Labs, Vienna, VA. Unpublished study	
Zirkin, B. (2000). Atrazine Effects on Testosterone and Androgen-Dependent Reproductive Organs in Peripubertal Male Rats. Unpublished study prepared by Novartis Crop Protection, Inc.	45058702
Minnema, D. (2001). Comparison of the LH Surge in Female Rats Administered Atrazine, Simazine or DACT via Oral Gavage for One Month: Final Report: Lab Project Number: 6117-398: 1198-98. Unpublished study prepared by Covance Laboratories, Inc.	45471002
Minnema, D. (2001). Comparison of the LH Surge in Female Rats Administered Atrazine, Simazine, and Diaminochlorotriazine (DACT) via Oral Gavage for One Month. Covance Laboratories, Vienna, VA. Laboratory report number: 6117398,	45471002
Ashby, J.; Tinwell, H. (2002). The Effects of Atrazine on the Sexual Maturation of Female Alderley Park-Wistar and Sprague-Dawley Rats: Final Report: Lab Project Number: 1775-02. Unpublished study prepared by Central Toxicology Laboratory.	45722401
Cooper RL, Stoker TE, Goldman JM, Parrish MB and Tyrey L (1996). Effect of atrazine on ovarian function in the rat. *Reprod Toxicol* **10**(4): 257-264	---
Cooper RL, Stoker TE, Tyrey L, Goldman JM and McElroy WK (2000). Atrazine disrupts the hypothalamic control of pituitary-ovarian function. *Toxicol Sci* **53**(2): 297-307	---
Cummings AM, Rhodes BE and Cooper RL (2000). Effect of atrazine on implantation and early pregnancy in 4 strains of rats. *Toxicol Sci* **58**(1): 135-143	---
Laws SC, Ferrell JM, Stoker TE and Cooper RL (2003). Pubertal development in female Wistar rats following exposure to propazine and atrazine biotransformation by-products, diamino-S-chlorotriazine and hydroxyatrazine. *Toxicol Sci* **76**(1): 190-200	---
Laws SC, Ferrell JM, Stoker TE, Schmid J and Cooper RL (2000). The effects of atrazine on female Wistar rats: an evaluation of the protocol for assessing pubertal development and thyroid function. *Toxicol Sci* **58**(2): 366-376	---
Stoker TE, Laws, S.C., Guidici, D. and Cooper, RL. (2000). The effect of atrazine on puberty in male Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. *Toxicol. Sci.* **58**: 50-59	---
Stoker TE, Guidici DL, Laws SC and Cooper RL (2002). The effects of atrazine metabolites on puberty and thyroid function in the male	---

Wistar rat. *Toxicol Sci* **67**(2): 198-206	

OEHHA examined the body of evidence relied upon by US EPA as the basis for formal identification of the triazines as causing reproductive toxicity (female reproductive and developmental endpoints). On the basis of the studies cited and described by US EPA and the effects identified above, OEHHA has concluded that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between the adverse reproductive effects in humans and the toxic agent in question is biologically plausible, thus meeting the sufficiency of evidence criteria in Section 25306.

OEHHA held a public comment period on the Notice of Intent to List in February and March 2014. Comments were submitted by Christian Volz and Stanley W. Landfair on behalf of Syngenta Crop Protection LLC. Six additional submissions, also included as attachments to the Syngenta submission, were made on behalf of Syngenta from the following individuals:

Tina E. Levine, Ph.D
James C. Lamb, IV, Ph.D
Gary Burin, Ph.D., MPH, DABT
Debra Edwards, Ph.D
Edwin F. (Rick) Tinsworth
John R. Fowle III, Ph.D., DABT

In addition, Ms. Pinky Kushner and Ms. Francesca Mariani provided short email notes in response to the Notice of Intent to List.

OEHHA reviewed all of the comments and accompanying materials submitted in the context of the regulatory criteria for listing chemicals under the authoritative bodies mechanism in Section 25306.

Comments from the individuals and groups listed above are grouped and numbered by topic, and responses follow below.

1. Comments in Support of Listing

1.1 Comment:

Two commenters expressed support for the listing of atrazine (Kushner) and the six triazines (Mariani).

Response:
OEHHA acknowledges the comments.

2. Comments on Formal Identification by US EPA of the Six Triazines as Causing Reproductive Toxicity

Five commenters (Levine, Edwards, Tinsworth, Fowle, Burin) identified themselves as former US EPA employees with knowledge of the Agency's regulatory procedures. The commenters objected to the listing of the triazines based on the authoritative bodies mechanism because, for the reasons itemized below, they argue that US EPA did not formally identify the triazines as causing reproductive toxicity. Syngenta made similar arguments, based largely on these five comments that, in addition to being submitted separately, were attachments to the Syngenta submission.

2.1 Comment:

- The statements by US EPA quoted by OEHHA and the use of developmental and reproductive endpoints as the basis for calculation of references doses by US EPA do not represent "conclusions" or "formal identification". (Syngenta)
- US EPA does not identify hazards, only endpoints for regulatory actions. (Levine, Burin)
- US EPA took a precautionary approach in identifying endpoints. (Fowle)
- US EPA has no statutory or regulatory mandate or authority to formally identify pesticides as toxicants. "There is no process for formally identifying pesticides as developmental or reproductive toxicants. Such designations are not the role of the EPA." (Tinsworth, Fowle[11])
- "There is no statutory mandate that requires or authorizes the Agency to develop and issue a list of developmental or reproductive toxicants." (Tinsworth)
- "OEHHA cannot rely on EPA's Hazard Identification and Risk Assessment Process." (Tinsworth)
- "EPA/OPP's scientifically rigorous and highly protective risk-based approach to regulating pesticides runs counter to the simplistic approach of labeling chemicals as "known to cause cancer" or "known to cause reproductive toxicity" under Proposition 65. The two approaches are so dissimilar that it is inappropriate to use isolated statements from evaluations of animal studies in the

[11] Fowle's comments state he agrees with the comments by Edwards and Tinsworth

absence of a firmly stated conclusion, as the basis for designating a chemical as a reproductive toxicant for purposes of Proposition 65". (Edwards, Fowle)

- "Experience has shown that risk assessments conducted for one purpose are not necessarily appropriate for other purposes." (Fowle)

Response:

Proposition 65 provides that "[a] chemical is known to the state to cause … reproductive toxicity within the meaning of this chapter if … a body considered to be authoritative by [the state's qualified] experts has formally identified it as causing … reproductive toxicity".[12] Implementing regulations define in Section 25306(d) what constitutes formal identification by an authoritative body as causing reproductive toxicity:

"For purposes of this section a chemical is 'formally identified' by an authoritative body when the lead agency determines that:

(1) the chemical has been included on a list of chemicals causing …reproductive toxicity issued by the authoritative body; or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes … reproductive toxicity; or has otherwise been identified as causing … reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action."[13]
(2) And the list, document or report meets the criteria in section 25306(d)(2).

The Final Statement of Reasons (FSOR) accompanying Section 25306, and relevant case law interpreting Proposition 65, make clear that OEHHA is the entity that makes the determination whether these chemicals have been formally identified as causing reproductive toxicity for purposes of Proposition 65[14,15]. That determination need not be made by the authoritative body, in this case US EPA[16]. *OEHHA* must conclude that the authoritative body's formal identification of the chemical as causing reproductive toxicity meets the criteria in Section 25306. OEHHA can make its determination based on the document issued by the authoritative body. OEHHA can also make its determination on the entire scientific record on which the authoritative body relied; including the scientific literature relied on by the authoritative body and OEHHA's knowledge of the

[12] Health and Safety Code section 25249.8(b).
[13] Title 27, Cal Code of Regs., section 25306(d)(1)
[14] OEHHA has been designated by Executive Order of the Governor as the Lead Agency pursuant to Health and Safety Code section 25249.12 and Title 27, Cal. Code of Regs., section 25102(o).
[15] Title 27, Cal Code of Regs, section 25306(c).
[16] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264

authoritative body's methodology[17]. The FSOR for Section 25306 indicates that, because an entity has been designated as an authoritative body, "…there is a presumption that the authoritative body properly applied the criteria."[18] In making its determination that the triazines have been formally identified by US EPA as causing female reproductive toxicity and developmental toxicity, OEHHA relied on the US EPA documents noted above and the underlying scientific literature relied on by US EPA.

As discussed above, the quoted statements by US EPA that the triazines cause reproductive and developmental toxicity constitute the conclusions of the authoritative body that the chemical causes reproductive toxicity. Further, the US EPA's decision to rely on certain developmental and reproductive endpoints as a basis for adopting RfDs for triazines as a final action further demonstrates that the triazines have been "otherwise identified" by the authoritative body as causing reproductive and developmental toxicity.

The US EPA documents identified by OEHHA as providing formal identification of these triazines as causing reproductive toxicity (US EPA 2002b; 2005; 2006a,b,c,d) meet the criteria in Section 25306(d)(2) that:

> "[T]he list, report, or document specifically and accurately identifies the chemical, and has been … [p]ublished by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency, or…otherwise set forth in an official document utilized by the authoritative body for regulatory purposes"

Several of the comments are premised on US EPA not having a process for "formally identifying" chemicals as causing reproductive toxicity, and not having a "mandate" to formally identify chemicals as causing reproductive toxicity or create a list of chemicals causing reproductive toxicity. There is no requirement in Proposition 65 or the implementing regulations that the authoritative body have such a process or mandate. The law and implementing regulations clearly contemplate that OEHHA will rely on the conclusions and findings of the authoritative body. Similarly, there is no requirement that the authoritative body develop and issue a list of chemicals causing developmental or reproductive toxicity or that it make its identification of the reproductive toxicity of a chemical in any specific manner. Scientific organizations such as US EPA are generally not focused on creating a list of chemicals known to cause reproductive and developmental toxicity. Settled law established that there are no particular words that

[17] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1280-1281
[18] Final Statement of Reasons for Section 25306 (formerly 12306), page 25 and *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1283

the authoritative body must use in making its determination and OEHHA may review the entire record before the authoritative body to determine whether the criteria in the Proposition 65 regulations have been met.[19]

The FSOR accompanying Section 25306 clearly contemplates exactly the situation that is presented here, where an identified authoritative body does not necessarily make determinations in a manner identical to Proposition 65. The FSOR explains that, for many scientific organizations, "[h]azard identification is simply one step toward the ultimate determination of a regulatory *exposure limit, tolerance, level*, etc."[20]. These scientific organizations, including US EPA, often are focused on determining endpoints of toxicity and developing what they believe to be appropriate exposure limits or tolerances for a chemical based on those endpoints. When the endpoints identified as providing the appropriately protective exposure limits or tolerances are the result of reproductive toxicity, US EPA must first "identify a chemical as a . . . reproductive hazard with finality," i.e., it must determine the "regulatory endpoint" that is at issue, and that "identification will be sufficient indication of a 'final action' on the issue of hazard identification to conclude that the chemical has been 'formally identified'."[21] Thus, under Proposition 65, US EPA's statement of its conclusions about reproductive and developmental harm caused by the triazines, and its identification of female reproductive and developmental endpoints as the basis for setting reference doses, constitute a hazard identification that represents the "formal identification" of the chemical as causing reproductive toxicity (female reproductive and developmental endpoints). In fact, as noted correctly by one of the commenters, "EPA uses the hazard identification step to review available animal toxicity studies and identify adverse effects which may present potential or possible risk in humans." (Tinsworth) This identification of the adverse effects posed by a chemical constitutes the hazard identification which is the basis for the Proposition 65 listing.

OEHHA has determined that US EPA has concluded that the triazines cause developmental and reproductive toxicity and has "otherwise identified" these chemicals "as causing reproductive [including developmental] toxicity", as those terms are used in the regulations[22]. OEHHA has further determined that the adoption by US EPA of standards (reference doses, or RfDs) based on female reproductive and developmental endpoints of toxicity constitutes, for purposes of Proposition 65, identification by US EPA of the chemicals as causing those endpoints. Finally, OEHHA has reviewed the US EPA documents cited above and the scientific literature and record before the US

[19] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1283-1284; *Western Crop Protection Association v Davis* (2000) 80 Cal.App. 4th 741, 745-748
[20] FSOR for section 25306 (formerly 12306) at page 11 (emphasis added).
[21] *Ibid*.
[22] Title 27, Cal Code of Regs, section 25306(d)(1)

EPA and has concluded that the US EPA's determinations meet the criteria set out in section 25306 of the regulations.

The fact that the authoritative body drew its conclusions and took its actions under different authority and for different regulatory purposes does not prevent OEHHA from relying on its conclusions and actions as a basis for formal identification under Proposition 65[23]. Although OEHHA agrees that risk assessments conducted for one purpose are not necessarily appropriate for other purposes, Proposition 65 explicitly requires OEHHA to rely on identification of a reproductive hazard by a designated authoritative body[24]. US EPA is a designated authoritative body[25] and, as noted above, US EPA stated repeatedly in several documents that the triazines cause reproductive and developmental toxicity in animals. For example, the statement that "EPA has determined that the triazine pesticides (with a common mechanism group of atrazine, propazine, simazine and their chlorometabolites) have common [sic] mechanism of suppression of LH surge and consequent developmental and reproductive effects" is clearly a conclusion that these chemicals cause reproductive and developmental toxicity, even if the term "conclusion" is not explicitly used.

2.2 Comment:

- Triazines are currently under re-evaluation by US EPA and are scheduled for reregistration review in 2015. (Edwards, Burin, Levine, Syngenta, Fowle)

Response:

OEHHA notes that reregistration of pesticides is an iterative process and that all registered pesticides are subject to re-review at intervals not to exceed 15 years:

> **"**EPA will review each registered pesticide at least every 15 years to determine whether it continues to meet the FIFRA standard for registration.[26]**"**

The most recent Reregistration Eligibility Decisions (REDs) on the triazines were published in 2006. OEHHA notes that US EPA has stated that "[a]trazine will begin registration review, EPA's periodic re-evaluation program for existing pesticides, in mid-2013"[27]. No further information on the status of that process has been made publicly available. Under its specified procedure, US EPA is not obliged to complete its re-review of triazines until 2021. Until the documents published in 2006 are superseded by

[23] *Western Crop Protection v Davis* (2000) 80 Cal.App.4th 741
[24] Health and safety Code section 25249.8(b)
[25] Title 27, Cal. Code of Regs., section 25306(l)(4)
[26] http://www2.epa.gov/pesticide-reevaluation/registration-review-process
[27] US EPA Atrazine Updates. Available at http://www.epa.gov/pesticides/reregistration/atrazine/atrazine_update.htm

subsequent reviews by the authoritative body, OEHHA must rely upon the conclusions and actions by the authoritative body documented in the most recent relevant publications. When revised REDs are available at some point in the future, OEHHA will consider whether they affect the listing status of the triazines. In fact, there is a provision in the regulations that expressly allows for reconsideration of a listing decision in such a circumstance:

> "Subsequent to the addition of a chemical determined to have been formally identified by an authoritative body as causing … reproductive toxicity to the list of chemicals known to the state to cause … reproductive toxicity, the lead agency shall reconsider its determination that the chemical has been formally identified as causing … reproductive toxicity if the lead agency finds:
> (1) there is no substantial evidence that the criteria identified in … subsection (g) have been satisfied, or
> (2) *the chemical is no longer identified as causing … reproductive toxicity by the authoritative body*."[28] (emphasis added)

3. Comments that the animal data cited by US EPA do not meet the requirements of Title 27, Cal Code of Regs., section 25306(g)(2)

Several comments were made regarding the extent to which the sufficiency of evidence criteria in Section 25306(g)(2) were met. Syngenta raised the issue under the general heading:

> "The animal studies referenced in the US EPA documents cited in the NOIL do not satisfy the requirement of 27 CCR section 25306(g) that such studies be sufficient evidence to indicate that adverse reproductive effects in humans are biologically plausible".

Various comment letters submitted on behalf of Syngenta and attached to Syngenta's comments addressed the sufficiency of the evidence issue.

The sufficiency of evidence criteria are set out in Section 25306(g):

> (g) "For purposes of this section, "as causing reproductive toxicity" means that either of the following criteria have been satisfied:
> (1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, *or*

[28] Title 27, Cal. Code of Regs., section 25306(j) (emphasis added)

(2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."[29]

3.1 Comment:

"…[I]t is clear that U.S. EPA, the authoritative body, did not itself review the animal studies cited in the NOIL to determine whether they were sufficient evidence to conclude that the chlorotriazines will cause the same effects in humans. … it simply is not possible for OEHHA to conclude that U.S. EPA, the authoritative body, reached a conclusion that the animal data satisfy the criteria of 27 CCR section 25306(g)." (Syngenta, p. 6)

Response:

As noted previously, OEHHA, as the Lead Agency for implementation of Proposition 65, makes the determination whether or not the criteria in Section 25306(g) are met. US EPA does not have to reach any such conclusion. [30,31,32] There is no requirement that US EPA consider Proposition 65 or its implementing regulations in carrying out its regulatory activities, much less that US EPA be required to follow them. However, as discussed in the response to comment 3.2 below, in this instance US EPA did conclude that adverse reproductive effects are possible in humans, which is equivalent to concluding that an association between adverse reproductive effects in humans and the atrazines is biologically plausible.

3.2 Comment:

"EPA is not attempting to determine whether a pesticide should be listed or formally identified as being known to cause effects in humans. Rather, EPA uses the hazard identification step to review available animal toxicity studies and identify adverse effects which may present potential or possible risk in humans." (Tinsworth)

"…the agency simply assumed that the effects observed were potentially relevant to humans, and then proceeded to apply its risk-based methodology to ensure that humans would never be exposed to levels of the chemicals that could possibly cause

[29] Title 27, Cal Code of Regs., section 25306(g)
[30] *Western Crop Protection v Davis* (2000) 80 Cal.App.4th 741
[31] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264
[32] Title 27, Cal Code of Regs., section 25306(c)

any adverse effect, even in the hypothetical worst-case that humans are equally or more susceptible to the adverse effects in question." (Syngenta, p. 6)

"The documents contain various statements indicating that the effects have been observed in animals, and that EPA is regulating the triazines on the basis of such effects on the assumption that similar effects in humans are possible. The documents nowhere state that EPA has concluded that the triazines *will* cause such effects in humans, only that EPA believes such effects are ***possible***..."(Edwards)

Response:

It is beyond dispute that chemicals must be listed under Proposition 65 if there is sufficient evidence of reproductive (including developmental) toxicity in animals[33]. There is no requirement in Proposition 65 or the implementing regulations that the authoritative body must conclude that reproductive or developmental toxicity *will* occur in humans. Once an authoritative body has determined that reproductive or developmental toxicity has been demonstrated in animals, it is routinely presumed by scientific bodies that, absent sufficient evidence to the contrary, adverse reproductive or developmental effects will also occur in humans. OEHHA has determined that the US EPA conclusions that satisfy the identification criteria in Section 25306, are based on sufficient data in animals. Once the identification criteria are met, OEHHA then determines whether it is biologically plausible that the effects demonstrated in animals could occur in humans[34,35].

Biological plausibility as used in Section 25306(g)(2) refers to the long-recognized scientific fact that adverse effects in animals as a result of exposure to a toxic chemical are generally predictive of adverse effects in humans exposed to that chemical. This is an explicit assumption underlying the use of animal data in toxicity risk assessment by the US EPA:

> "First, it is assumed that an agent that produces an adverse developmental effect in experimental animal studies will potentially pose a hazard to humans following sufficient exposure during development. This assumption is based on the comparisons of data for agents known to cause human developmental toxicity,

[33] *AFL-CIO v Deukmejian* (1989) 212 Cal.App. 3rd 425; *Western Crop, supra*, 80 Cal.App.4th 741; *Exxon Mobil, supra*, 169 Cal.App.4th 1264.
[34] Title 27, Cal Code of Regs., section 25306(c) and (g)(2)
[35] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1288-1289

which indicate that, in almost all cases, experimental animal data are predictive of a developmental effect in humans." [36]

"An agent that produces an adverse reproductive effect in experimental animal studies is assumed to pose a potential reproductive threat to humans. This assumption is based on comparisons of data for agents that are known to cause human reproductive toxicity. In general, the experimental animal data indicated adverse reproductive effects that are also seen in humans."[37]

In this case, OEHHA has concluded that the experimental animal studies on which US EPA relied indicate that there are sufficient data, taking into account all of the factors set forth in Section 25306(g), to indicate that adverse female reproductive and developmental effects are biologically plausible in humans. In reaching that conclusion, OEHHA also considered arguments made by the commenters that effects seen in animals were not biologically plausible in humans, as will be discussed further below in responses to comments in the remainder of Section 3.

OEHHA agrees with commenter Edward's assertion that, in this instance, the authoritative body explicitly expressed the same conclusion as that reached by OEHHA ("EPA believes such effects are possible [in humans]"). US EPA's position that reproductive and developmental toxicity seen in animals is biologically plausible in humans is also made clear by statements such as:

"In particular, the triazine-mediated changes in the HPG relating to neuroendocrine and neuroendocrine-related developmental and reproductive toxicity *are considered relevant to humans*…" (US EPA, 2006b: Triazine Cumulative Risk Assessment, page 4) (emphasis added).

3.3 Comment:

Under the heading "Mechanism of Action: Suppression of LH Surge in Sprague Dawley Rats", Dr. Lamb commented that "…the hormonal alteration is not, in and of itself, an adverse effect and is described by the Agency as 'a precursor event for the reproductive effects' in rats, not humans". (US EPA 2011, p. 14)..."

[36] US EPA Guidelines for Developmental Toxicity Risk Assessment (1991). Federal Register 56(234):63798-63826 (page 1). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162#Download

[37] US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996). Federal Register 61(212):56274-56322 (page 2). Available at http://www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm

The same comment is made by Volz (Syngenta Attachment A, p. 8, 9), and in the Syngenta Science Paper (Attachment B, pgs. 4, 6, 10, 12, 29)

Response:

The citation provided by Dr. Lamb as (US EPA 2011, p. 14) is:

> US Environmental Protection Agency (US EPA). 2011. Reevaluation of the human health effects of atrazine. Review of Cancer Epidemiology, Non-cancer experimental animal and in vitro studies and drinking water monitoring. Health Effects Division, Environmental Fate and Effects Division in collaboration with the Office of Research and Development. Presented on July 26-29, 2011.

Dr. Lamb did not provide a copy of the cited document. The identical citation is provided in Attachment B to the comments by Syngenta, identified as (US EPA 2011a). A copy of a document identified as US EPA 2011a was also provided to OEHHA by Syngenta. That document is titled:

> "FIFRA Scientific Advisory Panel (SAP) Open Meeting
> Reevaluation of the Human Health Effects of Atrazine:
> Review of Non-Cancer Effects and Drinking Water Monitoring Frequency and Cancer Epidemiology"

Although the passage quoted by Dr. Lamb does not appear on page 14 of the document provided by Syngenta and identified as US EPA 2011a, OEHHA has retrieved a document titled:

> "Re-Evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and *In vitro* Studies and Drinking Water Monitoring Frequency**"**[38]

This document was presented jointly to the FIFRA Scientific Advisory Panel by the US EPA Office of Pesticide Programs Health Effects Division and Environmental Fate and Effects Division in collaboration with the Office of Research and Development on July 26-29, 2011. This document appears to be the one cited by Dr. Lamb. Although the exact quotation provided by Dr. Lamb does not appear on page 14 of this document, a

[38] Re-Evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and *In vitro* Studies and Drinking Water Monitoring Frequency. Presented Jointly To The FIFRA Scientific Advisory Panel By: U.S. Environmental Protection Agency Office of Pesticide Programs Health Effects Division and Environmental Fate and Effects Division in collaboration with the Office of Research and Development. Presented On: July 26-29, 2011. Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2011-0399-0013

similar statement appears in the legend to a diagram on that page which pertains only to "LH Suppression and Adverse Outcomes Observed in Rats". The legend states, in its entirety, that:

> "Atrazine-induced changes in the hormonal milieu lead to a cascade of effects on reproductive function in male and female rats. The decrease in LH *is a precursor event to reproductive effects* both on a quantitative (i.e., occurs at lower doses) and temporal basis (occurs after 4 days of exposure). An atrazine related suppression of suckling-induced prolactin release in the lactating dams, is another hormonal change leading to an adverse effect (prostatitis) in the rat animal model." (Emphasis added.)

Assuming this is the passage Dr. Lamb referenced, it makes clear that the hormonal alteration is a precursor effect that leads to adverse reproductive effects in experimental animals. That conclusion constitutes an identification of the chemical as causing reproductive toxicity in animals. While the statement does not address whether the effects being described in rats are biologically plausible in humans, as noted previously, US EPA's position is that "[a]n agent that produces an adverse reproductive effect in experimental animal studies is assumed to pose a potential reproductive threat to humans. This assumption is based on comparisons of data for agents that are known to cause human reproductive toxicity. In general, the experimental animal data indicated adverse reproductive effects that are also seen in humans."[39]

Moreover, the diagram and its legend form part of the section of the document titled "Mode of Action (MOA) and Adverse Health Outcomes" (Section 2.3, beginning on page 12). The Agency's position on the relevance of the data in rodents to human health risk assessment is clearly stated elsewhere in that section:

> "For most pesticides, there is little information on the mode of action and even fewer with epidemiology studies that can be used in the risk assessment process. As such, the Agency makes assumptions about the relevance of animal findings to humans and quantitative animal to human extrapolation. *In the case of atrazine, the wealth of data across many scientific disciplines allows for a highly refined assessment for atrazine using MOA [mechanism of action] understanding, human relevance of animal studies informed qualitatively by epidemiology studies, and refined analysis of critical durations of exposure*." (p. 12). (emphasis added)

[39] US EPA Guidelines for Reproductive Toxicity Risk Assessment (1996). Federal Register 61(212):56274-56322 (page 2). Available at http://www.epa.gov/raf/publications/guidelines-reproductive-tox-risk-assessment.htm

> "In the course of the current evaluation**,** *the Agency identified an effect of atrazine on reproductive function in both male and female rats.* These effects provide insight into evaluating the vulnerability of specific lifestages such as sexual development, puberty, and the perturbation of adult reproductive performance (including premature aging). *These effects can be linked to the atrazine-induced changes in LH secretion.* Consequently, *the Agency will continue to use changes in LH secretion as the basis of the atrazine risk assessment*." (p.13). (emphasis added)

These statements demonstrate that US EPA considers adverse reproductive and developmental effects of atrazine (and, by extension, all of the triazines in the common mechanism class) in animals to be directly relevant to humans and to provide an appropriate basis for establishing health-protective standards for human exposures.

3.4 Comment:

"Reproductive effects are observed only in studies where atrazine is administered by gavage resulting in high plasma concentrations that could not occur in humans from dietary, drinking water or occupational exposure to atrazine." Lamb (p. 2).

The same comment is also made in Syngenta Attachments A (p. 7, 10), B (Syngenta Science Paper, p. 4, 10, 29), and G (Burin, p. 2):

- "The route of exposure is particularly important since high bolus doses of atrazine are associated with suppression of the LH surge, but extremely high dietary exposures are required to produce a similar effect…" (Lamb, p. 3)
- "…The reproductive effects noted by OEHHA have been observed in gavage studies, but have not been reported in dietary studies at comparable doses…" (Lamb, p. 5;, Syngenta Attachment B, p. 4).
- "…A number of recent studies have been conducted to better understand the pharmacokinetics (PK) of atrazine …These studies have shown that administration by gavage results in rapid, high plasma concentrations of atrazine and its metabolites, while dietary intake at similar doses resulted in lower peak and total plasma concentrations of atrazine and its metabolites …The gavage route of exposure results in a bolus dose to the animal, which is immediately available for absorption and distribution. In contrast, animals exposed to atrazine in the diet have a slow steady exposure, resulting in a lower, more constant plasma levels. Given the rapid elimination of atrazine and metabolites, they do not build up in the body, so there is no opportunity for plasma concentrations to

reach the levels achieved by gavage…" (Lamb, p. 5; also discussed in Syngenta Attachments A, p. 7 and B, pp. 5, 14, 22-28).

Response:

The commenters acknowledge that reproductive effects in animals result from oral administration of atrazine. The relevant consideration is therefore whether those effects are biologically plausible in humans under Section 25306(g)(2). The commenters offer their opinion about the likelihood that a level of exposure sufficient to cause an adverse reproductive effect in humans could occur from dietary, drinking water or occupational exposure to atrazine. This does not address whether there is a *biological* limit on the amount of atrazine a human can ingest either as a bolus or over a more extended period of time. Biological plausibility, as used in the Proposition 65 regulations, is not dependent on the extent of the anticipated current exposures that may occur. The assumed absence of current exposures sufficient to cause reproductive toxicity in humans does not address the question of whether such effects will occur if humans are exposed to higher levels of the chemicals. Thus, the commenters have failed to provide any support for their stated opinion that adverse effects in humans are not *biologically* plausible. While it is to be hoped that actual environmental and occupation exposures of humans to triazines are below levels that will cause reproductive and developmental toxicity, Section 25306 does not require or permit OEHHA to decline to list a chemical that meets the statutory and regulatory requirements for listing for that reason.[40]

As a point of clarification, the commenters referred to oral gavage and oral dietary exposure as different routes of exposure, rather than different patterns of exposure, when contrasting bolus administration of atrazine with dietary exposure. Both of these exposures occurred by the oral route, only the patterns of exposure were different.

3.5 Comment:

The biological relevance to humans of findings of reproductive hormone effects in the rats studied was questioned:

- "…Significant differences exist between the rat and human female reproductive hormone cycle…" (Lamb, p. 2)

  "The common MOA for chlorotriazine herbicides relied on by EPA for risk assessment is suppression of the luteinizing hormone (LH) surge that is part of the hormonal cascade that comprises the rat estrous cycle. This suppression of the LH surge has been observed in several animal models, but the Sprague Dawley (SD) strain of rat is the most sensitive. The observed differences in

[40] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, 1290

response to atrazine raise the question about whether this strain of rat is appropriate for assessing potential human health effects." (Lamb, p. 2; the same type of comment is also made in Syngenta Attachments A [p. 9] and B [pp. 4, 5, 11]).

"… atrazine does not directly affect LH secretion from the pituitary in the rat… Given the fact that the ovary and pituitary play a more central role in the hormonal control of the menstrual cycle in humans, this suggests that atrazine should not affect the LH surge in humans…" (Lamb, p. 3; the same comment is also made in Syngenta Attachment B, p. 11).

- "Considering the current body of evidence on the MOA for atrazine, it is apparent that the suppression of the LH surge is not relevant or biologically plausible in humans. The US EPA SAP [Scientific Advisory Panel] similarly concluded that:

  It seems unlikely that humans would ever experience the sorts of internal exposures necessary in rats to produce suppression of the LH surge (EPA SAP 2011, p. 84)…"

  (Lamb, p. 4; also presented in Syngenta Attachment A, p. 6)

Response:
While OEHHA must make the determination of biological plausibility under section 25306, in this case US EPA cited evidence that enabled it to conclude that it is biologically plausible that triazines pose a reproductive and developmental hazard to humans:

"Neuroendocrine effects are considered the critical endpoints for assessing the health effects of the CMG Triazines. The CMG triazines have been shown to lead to various endocrine-related changes as a result of an effect on the hypothalamic-pituitary-gonadal axis. The consequences of this action include a diminishment of hypothalamic gonadotrophin releasing hormone (GnRH) and norepinephrine levels. These triazines also increase dopamine level which can result in a diminished pituitary secretion of PRL [prolactin]. Therefore, the CMG triazines operate at the level of the hypothalamus. *In both humans and rats*, hypothalamic GnRH controls pituitary hormone secretion (e.g., luteinizing hormone and PRL)." (US EPA, 2006b: Triazine Cumulative Risk Assessment, p. 22 (emphasis added).

"In particular, the triazine-mediated changes in the HPG relating to neuroendocrine and neuroendocrine-related developmental and reproductive toxicity *are considered relevant to humans*, and these adverse effects were

identified as endpoints for the exposure scenarios selected for consideration in the quantitative cumulative assessment." (US EPA, 2006b: Triazine Cumulative Risk Assessment, p. 4) (emphasis added)

Those conclusions are based on data from studies in animal species and strains that include the Sprague-Dawley rat. While OEHHA recognizes that there are differences between rodent and human reproductive physiology, US EPA considered these differences and concluded, on the basis of animal data, that the triazines cause reproductive and developmental toxicity and further concluded that those data are relevant to humans. OEHHA has examined the record before the US EPA and has determined that there is sufficient evidence to support US EPA's conclusions and that the data meet the criteria pursuant to Proposition 65. Although the commenter considers the differences between the rat and human female reproductive hormone cycle to be significant, OEHHA is not permitted to substitute its scientific judgment for that of the authoritative body[41], nor can OEHHA substitute the judgment of other scientists for that of the authoritative body.

The statement quoted by the commenter from the US EPA Scientific Advisory Panel (SAP) 2011 report – *"It seems unlikely that humans would ever experience the sorts of internal exposures necessary in rats to produce suppression of the LH surge.* (EPA SAP 2011, p. 84)…" – is not consistent with the conclusion drawn by the commenter that "the suppression of the LH surge is not relevant or biologically plausible in humans." The US EPA SAP expressed an opinion that internal exposures to triazines in humans would likely not reach the levels necessary to produce suppression of the LH surge in rats. This is not a conclusion that the LH surge is not relevant or biologically plausible in humans. In fact, to the contrary, had the US EPA SAP considered that "suppression of the LH surge is not relevant or biologically plausible in humans", as asserted by the commenter, there would have been no reason for it to compare exposure levels in rodents and humans. As discussed above, US EPA expressly considers suppression of the LH surge in rodents *to be relevant to humans*. Additional data not considered by the authoritative body relevant to this issue will be discussed below in section 4.

3.6 Comment:

"… Because the signal for initiating the LH surge in humans is a feedback mechanism driven by estradiol released by the ovary, the reduction in GnRH is unlikely to impact the LH surge in humans..." (Lamb, p. 3)

[41] Final Statement of Reasons, Title 27 (formerly 22) Cal. Code of Regs., section 25306 (Formerly 12306). Available online at: http://www.oehha.ca.gov/prop65/law/pdf_zip/12306FSRFeb1990.pdf; ExxonMobil Corp. v. OEHHA (2009) 169 Cal.App.4th 1264; Western Crop Protection v Davis (2000) 80 Cal.App.4th 741.

Response:

Reduction in GnRH is relevant to reproductive function, including the LH surge, in humans. It has long been known that the preovulatory LH surge in humans will not occur in the absence of GnRH[42, 43]. Even if GnRH does not directly control the LH surge in humans as it does in rodents, it still appears to play several roles in the maintenance of a healthy ovarian cycle.

GnRH is produced by the hypothalamus in the brain. Reduced GnRH production in humans is the principle cause of functional hypothalamic amenorrhea (FHA), a common form of anovulation, or failure to ovulate. For example, in patients with depressed hypothalamic-pituitary-ovarian (HPO) activity who were not ovulating, ovulation and normal ovarian function were restored following cognitive behavior therapy to stimulate hypothalamic function[44]. This observation indicates that behavioral factors are involved in controlling ovarian activity in women, most likely through GnRH[45]. Thus, while feedback to the pituitary from the ovary via estradiol is an important control of the LH surge in humans, a reduction (or absence) of GnRH may lead to anovulatory menstrual cycles suggesting that GnRH is necessary for the LH surge in humans.

3.7 Comment:

"The loss of reproductive capability of human females is related to the reduced number of eggs in the aging ovaries, not the reduction in GnRH levels seen in aging SD rats (Chapin et al. 1996)[46]. Menopause is also associated with lower estrogen production leading to a lower estrogen to progesterone ratio - the direct opposite of what is seen in SD rats. Thus, there are several significant differences in the induction of the LH surge between rats and humans." (Lamb, p. 3; the same comment is also made in Syngenta Attachment B, pp. 4, 10, 12).

Response:

The comments refer to endpoints of female reproductive senescence (reduced GnRH levels in aging rats) that were not identified by OEHHA as supporting the formal

[42] Ferin M (1983). Neuroendocrine control of ovarian function in the primate. *J Reprod Fertil* **69**(1): 369-381.

[43] Crowley WF, Jr., Filicori M, Spratt DI and Santoro NF (1985). The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. *Recent Prog Horm Res* **41**: 473-531.

[44] Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R and Krohn MA (2003). Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. Fertil Steril 80(4): 976-981.

[45] Crowley WF, Jr., Filicori M, Spratt DI and Santoro NF (1985). The physiology of gonadotropin-releasing hormone (GnRH) secretion in men and women. *Recent Prog Horm Res* **41**: 473-531.

[46] Chapin, R.E., Stevens, J.T., Hughes, C.L., Kelce, W.R., Hess, R.A. and Daston, G.P. (1996). Endocrine modulation of reproduction. Fundam Appl Toxicol Jan;29(1):1-17.

identification of the triazines as causing reproductive toxicity[47]. Thus, the comments are not relevant to the listing to the triazines. In addition, although the commenters' conclusion that "…there are several significant differences in the induction of the LH surge between rats and humans…" is correct, the 'common mechanism' underlying the reproductive effects is suppression of the LH surge, which occurs in both rodents and humans. Finally, the comment states that there are significant differences in the induction of the LH surge between rats and humans and suggests that these differences are related to differences in reproductive senescence (aging and menopause) between rats and humans. Although there are differences in the induction of the LH surge in rats and humans, these differences are not related to aging and menopause, as the commenter suggests.

3.8 Comment:

Lamb (p.3) commented, "Although reproductively aged female SD rats have been shown to be sensitive to the effects of atrazine, younger animals are more resilient to the influences of atrazine on GnRH… which was acknowledged by the US EPA Scientific Advisory Panel (SAP):

> *An extensive hazard database, spanning all life stages from conception to adulthood for atrazine, indicates no unique susceptibility in the developing organism. Additionally, the proposed point of departure, based upon attenuation of the LH surge, appears to be protective against adverse reproductive/developmental outcomes such as delays in onset of puberty, disruption of ovarian cyclicity and inhibition of suckling-induced prolactin release. (EPA SAP 2011, p 14)"* (*Italics in original*)

The same comment is also made in Syngenta Attachment A (p. 9), and B (p. 13).

Response:

The commenters claim that the SAP acknowledged that younger animals are more resilient to the influences of atrazine on GnRH. This assertion is not supported by the quoted passage from the SAP provided by the commenter. Rather, the passage states the SAP's opinion that there is *"no unique susceptibility in the developing organism*," i.e., that the developing organism is no more sensitive to the adverse effects of atrazine than are mature animals. The passage does not indicate that the developing organism is *less sensitive* to the adverse effects of atrazine. Absence of greater sensitivity is not equivalent to greater resilience, since the developing organism that lacks unique

[47] Notice of Intent to List Atrazine, Propazine, Simazine and their Chlorometabolites, DACT, DEA and DIA. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilpkg41Triazines.html

sensitivity may simply be equally as sensitive as the mature organism. The opinion of the SAP is further clarified by other statements in the SAP document which indicate that there is no early age-related sensitivity to the triazines:

> *"The Panel agreed with the Agency's conclusion that exposure during the **earlier life stages does not appear to lead to greater sensitivity**, if one accepts the premise that the data on suppression of the LH surge is appropriate for use in making the comparisons... Given the **apparent lack of early age-related sensitivity to the neuroendocrine effects** that are driving the hazard assessment…"* (FIFRA-SAP, 2011)[48]. (bold emphasis added)

3.9 Comment:

Under the heading "Reproductive Toxicity and Consideration of Experimental Study Design" the commenter states:

> OEHHA specifically identifies several male and female reproductive endpoints as the basis for the Notice of Intent to list atrazine as a reproductive toxicant. These endpoints include: prolonged estrus in the dams (as discussed above), delayed ossification of certain cranial bones of fetuses, delayed vaginal opening (VO) in female pups, and delayed preputial separation (PPS) in male pups. As acknowledged by EPA at the Scientific Advisory Panel in July 2011, all of these effects all of these effects [sic] occur at doses greater than that associated with suppression of the LH surge:
>
> *The Agency will continue to use changes in LH secretion as the basis of the atrazine risk assessment. As such, any of the identified adverse outcomes would be protected since they occur at doses higher than those eliciting changes in LH* (US EPA 2011, p. 13)… Lamb (p. 4).

Response:

The statement by the commenter and the quoted passage both confirm that US EPA has identified atrazine as causing adverse reproductive outcomes (prolonged estrus, delayed ossification of cranial bones of fetuses, delayed vaginal opening in female pups). The commenter points out that these adverse female reproductive and developmental effects occur at levels that are higher than the level at which suppression of the LH surge occurs. It appears that the commenter is suggesting that OEHHA

[48] FIFRA-SAP (2011). SAP Minutes No. 2011-05. A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Re-evaluation of the Human Health Effects of Atrazine: Review of Non-Cancer Effects, Drinking Water Monitoring Frequency and Cancer Epidemiology. July 26 – 28, 2011 Meeting, FSAP. Held at the Environmental Protection Agency Conference Center, Arlington, VA

should ignore the indicated adverse female reproductive and developmental endpoints because they occur at higher levels than the LH surge effect. OEHHA cannot simply disregard these endpoints. Considered in the context of the entire relevant passage from the US EPA document cited by the commenter, of which only a portion is identified in the comment, it is clear that US EPA based its risk assessment on atrazine-induced changes in LH secretion because those changes are linked to adverse effects that are apparent at higher levels of exposure.

> "In the course of the current evaluation, the Agency identified an effect of atrazine on reproductive function in both male and female rats. These effects provide insight into evaluating the vulnerability of specific lifestages such as sexual development, puberty, and the perturbation of adult reproductive performance (including premature aging). These effects can be linked to the atrazine-induced changes in LH secretion. Consequently, the Agency will continue to use changes in LH secretion as the basis of the atrazine risk assessment. As such, any of the identified adverse outcomes would be protected since they occur at doses higher than those eliciting changes in LH"[49]

Under Proposition 65, all adverse reproductive and developmental effects are taken into consideration in identification of a reproductive hazard for purposes of listing a chemical. After the chemical has been listed, if OEHHA calculates a regulatory maximum allowable dose level ("MADL") pursuant to Section 25805, the agency will then focus on the lowest level of exposure at which specific endpoints of reproductive or developmental toxicity occur.[50]

Further, the commenter's statement that "OEHHA…identifies…male…reproductive endpoints as the basis for the Notice of Intent to list atrazine" is incorrect. The Notice of Intent to List specifically identified female reproductive toxicity and developmental toxicity as the relevant endpoints[51].

3.10 Comment:

[49] Re-Evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and *In vitro* Studies and Drinking Water Monitoring Frequency. Presented Jointly To The FIFRA Scientific Advisory Panel By: U.S. Environmental Protection Agency Office of Pesticide Programs Health Effects Division and Environmental Fate and Effects Division in collaboration with the Office of Research and Development. Presented On: July 26-29, 2011. (Page 13). Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2011-0399-0013

[50] Title 27, Cal Code of Regs., section 25803,

[51] Notice of Intent to List: Atrazine, Propazine, Simazine and their Chlorometabolites DACT, DEA and DIA. Available at http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilpkg41Triazines.html

"The precursor event, suppression of the LH surge, has been only been (*sic*) observed in dietary studies at doses greater than 400 ppm, which is considered higher than the maximum tolerated dose and is associated with significant effects on body weight and body weight gains (Chapin et al. 1996[52], Simpkins et al. 2011[53]) The changes in body weight are considered signs of systemic toxicity and in a reproductive study would clearly represent maternal toxicity which, as stated in the Prop 65 regulations, should be considered in judging the biological plausibility for humans…"
Lamb (p. 5).

The same comment is also made in Syngenta Attachment A (p. 6, 7).

Response:
The commenters are in error when they state that LH surge has only been observed in dietary studies at doses greater than 400 ppm. In fact, US EPA identified 3.65 mg/kg/day, resulting from exposure to 50 ppm in diet for 26 weeks, as representing the lowest observed adverse effect level (LOAEL), based on estrous cycle alterations and LH surge attenuation[54]. Further, the publications cited by the commenters in support of their claim that the studies demonstrate maternal toxicity, provide no data on body weight or weight gain in rodents treated with atrazine and therefore do not demonstrate maternal toxicity. In particular, the paper by Chapin et al. (1996) states that "the MTD [maximum tolerated dose] in chronically fed rats is about 40 mg/kg". This provides no basis whatsoever for inferring systemic toxicity at the LOAEL of 3.65 mg/kg/day identified by US EPA. Finally, the endpoints identified in the paper by Chapin et al. represent evidence of female *reproductive toxicity, not developmental toxicity*. Maternal toxicity is not relevant in a study of female reproductive endpoints, so there is simply no basis on which to infer from the Chapin study that maternal toxicity would occur in a developmental toxicity study.

3.11 Comment:
"… the observation of delayed ossification of cranial bones is not considered an adverse effect, such as a malformation. Second, as noted by US EPA (2006), these developmental delays were seen in conjunction with a decreased body weight gain, which suggests maternal toxicity." Lamb (p. 5).

The same comment is also made in Syngenta Attachment A (p. 6).

[52] Chapin, R.E., Stevens, J.T., Hughes, C.L., Kelce, W.R., Hess, R.A. and Daston, G.P. 1996. Endocrine modulation of reproduction. Fundam Appl Toxicol Jan,29(1):1-17.
[53] Simpkins, J. W., Swenberg, J.S., Weiss, N., Brusick, D., Eldridge, J. C., Stevens, J. T., Handa, R. J., Hovey, R. C., Plant, T. M., Pastoor, T. P. and Breckenridge, C. B. 2011. Atrazine and breast cancer: A framework assessment of the toxicological and epidemiological evidence. Toxicol. Sci., 123,441-459.
[54] US EPA (2002a). Atrazine (PC Code: 080803). Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document (Second Revision). April 11, 2002. (page 27).

"There was evidence of maternal toxicity in animals administered high doses of the chlorotriazines by gavage. Maternal toxicity was evidenced by reduced maternal body weight gain that was corrected for fetal body weight effects. … Ossification delay occurs with deficits in fetal body weight and represents a transient effect of maternal toxicity (Carney and Kimmel, 2007)[55]". Syngenta Attachment B (p. 16).

Response:

Dr. Lamb's opinion that delayed ossification of cranial bones is not considered an adverse effect is inconsistent with the judgment of the authoritative body, as expressed in the US EPA Guidelines for Developmental Toxicity Risk Assessment.[56] In the table titled "Endpoints of Developmental Toxicity: Altered Survival, Growth, and Morphological Development", US EPA specifically identifies anatomical and skeletal variations as relevant developmental endpoints, as follows:

> "No. and percent offspring with external, visceral, or skeletal variations/litter
> No. and percent offspring with variations/litter
> No. and percent litters having offspring with variations
> Types and incidence of individual variations
> Individual offspring and their malformations and variations
> (grouped according to litter and dose)" (page 11).

In that same document, US EPA clarifies that delayed ossification can be considered an anatomical variation and a relevant endpoint of developmental toxicity:

> "Although a dose-related increase in malformations is interpreted as an adverse developmental effect of exposure to an agent, the biological significance of an altered incidence of *anatomical variations* is more difficult to assess, and must take into account what is known about developmental stage (*e.g., with skeletal ossification*)" (page 13). (emphasis added)

Thus, it is clear that US EPA was consistent with its own adopted guidelines when it concluded that "[d]elayed ossification of certain cranial bones in fetuses" US EPA (2006a)[57], "[d]elayed or lack of ossification of several sites" US EPA (2002b)[58] and

[55] Carney, E.W. and Kimmel, C.A. (2007). Interpretation of Skeletal Variations for Human Risk Assessment: Delayed Ossification and Wavy Ribs. Birth Defects Research (Part B) 80:473–496.
[56] US EPA Guidelines for Developmental Toxicity Risk Assessment (1991). Federal Register 56(234):63798-63826 (page 1). Available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23162#Download
[57] US EPA (2006a). Decision Documents for Atrazine. US EPA OPPTS. Available at http://www.epa.gov/pesticides/reregistration/REDs/atrazine_combined_docs.pdf

"unossified teeth, head, centra vertebrae, sternabrae, and … rudimentary ribs" US EPA (2006d)[59] were adverse developmental effects that could serve as the basis for RfDs.

OEHHA was unable to identify any support in the US EPA document cited by Dr. Lamb for the statement that US EPA noted "these developmental delays were seen in conjunction with a decreased body weight gain, which suggests maternal toxicity." [60]

In contrast, that document states:

> "In a prenatal developmental toxicity study with DACT in rats, developmental effects were seen in the absence of maternal toxicity. The maternal NOAEL was 25 mg/kg/day based on statistically significant decrease in body weight gain at 75 mg/kg/day (LOAEL). The developmental NOAEL was 2.5 mg/kg/day based on increased incidence of incompletely ossified parietals, interparietals and unossified hyoids at 25 mg/kg/day (LOAEL)." (US EPA, 2006b: Triazine Cumulative Risk Assessment, p. 33)

It is therefore clear that US EPA views delayed ossification as a developmental endpoint and considered factors such as maternal toxicity and its relationship to delayed ossification before formally identifying the triazines as causing developmental toxicity. This approach is consistent with that suggested by Carney and Kimmel[61], that "these minor variations would not generally be considered adverse in and of themselves but should be interpreted in the context of other maternal and fetal findings". Finally, it should also be noted that the Carney and Kimmel paper cited by the commenter represents the judgment of two individual scientists. As noted in the response to comment 3.5, if there is sufficient evidence before the authoritative body, OEHHA is not permitted to substitute its scientific judgment for that of the authoritative body, nor can OEHHA substitute the judgment of other scientists for that of the authoritative body.

3.12 Comment:

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[58] US EPA (2002b). Office of Pesticide Programs. Special Docket for Pesticide Reregistration Risk Assessments. Memorandum on ATRAZINE/DACT - Fourth Report of the Hazard Identification Assessment Review Committee. TXR NO. 0050592

[59] US EPA (2006d). Reregistration Eligibility Decision Document for Simazine. US EPA OPPTS. EPA 738-R-06-008. Available at http://www.epa.gov/opp00001/reregistration/status_page_s.htm

[60] US Environmental Protection Agency (US EPA, 2006b). Triazine Cumulative Risk Assessment (March 28, 2006). Available at http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#triazine

[61] Carney, E.W. and Kimmel, C.A. (2007). Interpretation of Skeletal Variations for Human Risk Assessment: Delayed Ossification and Wavy Ribs. Birth Defects Research (Part B) 80:473–496.

"Furthermore, in a recent review of all developmental toxicity studies, Scialli et al. (2014)[62] concluded that "[o]verall, data show that neither [atrazine] or its metabolites statistically significantly affected rat or rabbit embryo-fetal development even at dose levels producing maternal toxicity." Lamb (p. 5).

The same comment was made in Syngenta Attachments A (p. 6) and B (p. 16).

Response:
The commenters note that Scialli et al. conclude that overall, there are no adverse developmental effects from triazines. As documented in the introductory section to this response to comments, however, US EPA, has clearly reached the opposite conclusion. OEHHA has determined that US EPA's conclusion is supported by substantial scientific evidence in the US EPA record. OEHHA is not permitted to substitute its scientific judgment for that of the authoritative body, nor can OEHHA substitute the judgment of other scientists for that of the authoritative body.

3.13 Comment:
"I conclude that atrazine should not be listed by the State of California on the basis of reproductive toxicity. This conclusion is based on the study design parameters and other toxicological factors that are associated with the observation of reproductive effects in rats. When the route of administration, frequency and duration of exposure, and maternal toxicity are taken into consideration, the biological plausibility of these effects occurring in humans at typical or higher occupational exposures is not credible." Lamb (p. 6).

The same comment is also made by Syngenta Attachment B (p. 29).

Response:
The commenters interpret "typical or higher occupational exposures" of humans as relevant to the *biological* plausibility that adverse reproductive effects could occur in humans. As discussed above, this is not scientifically valid. Biological plausibility as used in the Proposition 65 regulations is not dependent on the extent of the current or anticipated human exposures to the chemical.[63]

4. Comments that data not considered by US EPA show that the requirements of Title 27, Cal Code of Regs., section 25306(g)(2) are not met

[62] Scialli, A., DeSesso, J. D. and Breckenridge, C. B. 2014. Developmental toxicity studies with atrazine and its major metabolites in rats and rabbits. J. Birth Defects Research (Part B) 00:1-16.
[63] *ExxonMobil Corp. v. OEHHA* (2009) 169 Cal.App.4th 1264

4.1 Comment:
"…Furthermore, since the 2002 and 2006 reports, new data have been developed and are being actively considered by the Agency"… "The new data provide even more information on the MOA to show that the reproductive effects seen in rats are not relevant to humans…" Lamb (p. 2).

Same comment by Volz pp. 6-8 and Volz (Syngenta Attachment A, p. 2, 4, 10-13), Syngenta Science Paper (Attachment B, p. 4, 5), Burin (p. 4) and Breckenridge (Syngenta Attachment K, pp. 1-2).

Response:
Section 25306(h) requires that "the lead agency shall find that a chemical does not satisfy the definition of 'as causing reproductive toxicity' if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not meet the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)". The commenters described several studies as having relevant data that were not considered by the authoritative body.

Most of the information cited by the commenters related to the use of the animal data and their relevance for human risk assessment has already been discussed in section 3 above. Other comments specific to data not considered by the authoritative body will be addressed in the remainder of this section.

4.2 Comment:
"Recent studies … further demonstrate that the effects observed in animal studies …are not sufficient evidence that similar effects in humans are biologically plausible," referring to Attachments H-L. (Syngenta, p. 7)

Response:
Attachment H does not provide information on recent studies. This attachment is a letter by Dr. Anthony Scialli citing a paper by Infurna et al. (1988)[64] investigating developmental toxicity of atrazine in rats and rabbits and a review by Scialli et al. (2014)[65] of reproductive and developmental toxicity studies of atrazine and its major metabolites DEA, DIA and DACT conducted between 1966 and 1992. The letter and the cited review present the authors' interpretation of these older studies. The review

[64] Infurna R, Levy B, Meng C, Yau E, Traina V, Rolofson G, Stevens J, Barnett J. (1988). Teratological evaluations of atrazine technical, a triazine herbicide, in rats and rabbits. J Toxicol Environ Health.;24(3):307-19.
[65] Anthony R. Scialli, John M. DeSesso and Charles B. Breckenridge (2014). Developmental Toxicity Studies with Atrazine and its Major Metabolites in Rats and Rabbits. Birth Defects Research (Part B) 101:199–214.

was also cited in comments by Dr. Lamb addressed above (Comment 3.12). As stated in the response to that comment, OEHHA must determine whether the conclusions of the authoritative body are supported by substantial evidence. If they are, OEHHA is not permitted to substitute its scientific judgment for that of the authoritative body nor can OEHHA substitute the judgment of other scientists for that of the authoritative body. Nothing in Attachment H changes OEHHA's determination that the US EPA's conclusions are supported by substantial evidence.

Attachment I is the abstract of a paper by Foradori et al. that had been submitted for publication. OEHHA subsequently retrieved and reviewed the published paper [66]. The abstract identifies adverse reproductive effects in rats resulting from bolus administration of atrazine, but not from dietary administration of an equivalent amount of the chemical. The authors conclude that "high bolus doses of ATR significantly reduced the preovulatory LH surge and the number of CL [corpora lutea] and ova shed" in Sprague-Dawley rats. The authors also conclude that "the effects of ATR on the LH surge and ovulation following bolus doses are highly unlikely to occur in humans exposed at low, temporally distributed, concentrations of ATR in drinking water." While these findings may be relevant to the likelihood that adverse effects will occur in humans under that specific exposure scenario, they do not suggest any biological reason why adverse effects would not be plausible in humans under exposure conditions comparable to those that cause such effects in rats. Biological plausibility as used in the Proposition 65 regulations is not dependent on the extent of current or anticipated human exposures.[67] Nothing in Attachment I changes OEHHA's determination that the US EPA's conclusions are supported by substantial evidence.

Attachment J is the abstract of a paper by De Sesso et al. that had been accepted for publication. OEHHA subsequently retrieved and reviewed the published paper[68]. The commenter states that "atrazine showed no adverse reproductive effects in rodents at maximum tolerated doses of ≈ [approximately] 40mg/kg/day in studies following U.S. EPA guidelines". However, the study reported that "small increases in abnormal sperm were noted at doses of 25 mg/kg/day and above, and reductions in testicular weights were noted after lactational exposure at 125 mg/kg/day". On that basis, the authors concluded that "although there were some effects of a high bolus dose of ATR on the development of the male reproductive system, the NOELs following prenatal (5

[66]Foradori,C.D., Coder,P.S., Tisdel, M., Yi,,K.D.,Simpkins, J.W., Robert J. Handa,R.J. and Breckenridge, C.B. (2014). The Effect of Atrazine Administered by Gavage or in Diet on the LH Surge and Reproductive Performance in Intact Female Sprague-Dawley and Long Evans Rats. Birth Defects Research (Part B) 101:262–275 (2014).

[67] *ExxonMobil Corp. v. OEHHA* (2009) 169 Cal.App.4th 1264

[68]DeSesso,J.M., Scialli, A.R., White, T.E.K.and Breckenridge, C.B. (2014). Multigeneration Reproduction and Male Developmental Toxicity Studies on Atrazine in Rats. Birth Defects Research (Part B) 101:237–253.

mg/kg/day) and postnatal (25 mg/kg/day) exposure were much higher than would be expected in humans under normal use conditions". The study did not assess the reproductive and developmental toxicity parameters that formed the basis for formal identification by US EPA of the triazines as causing reproductive toxicity. Therefore, the study provides no data that conflict with US EPA's formal identification of female reproductive and developmental toxicity on the basis of neurotransmitter and neuropeptide alterations at the level of the hypothalamus that, as noted above, US EPA considers the primary toxicological effects of regulatory concern, nor on developmental delays such as delayed vaginal opening and preputial separation in developing rats. Those effects were identified by US EPA as occurring at exposure levels below 40mg/kg/day. Nothing in Attachment J changes OEHHA's determination that US EPA's conclusions are supported by substantial evidence.

Attachment K is a letter by Breckenridge et al. that offers four reasons for opposing OEHHA listing the triazines:

1. *US EPA did not formally conclude that the chlorotriazines are human developmental and reproductive toxicants.*
   Response: As explained in the response to comment 2.2, there is no requirement in Proposition 65 or its implementing regulations that the authoritative body conclude that reproductive or developmental toxicity will occur in humans. OEHHA has determined that the US EPA conclusions concerning the reproductive and developmental toxicity of the triazines based on experimental animal data satisfy the identification criteria set forth in Section 25306.
2. *In 2011, the Scientific Advisory Panel of the USEPA advised EPA that a causal association between changes in LH surge peak and adverse fertility measures has not been made*.
   Response: It is the US EPA and not that agency's Scientific Advisory Panel that is identified as an authoritative body for purposes of Proposition 65[69]. The US EPA Charter for the Scientific Advisory Panel[70] states that "the duties of the [EPA] FIFRA SAP are solely to provide advice to the EPA". The comment cites to and quotes from the minutes of a meeting of the US EPA Scientific Advisory Panel identified in the text as having occurred from September 14-27, 2011. However, the citation provided for the minutes of the meeting identify it as having occurred on September 14-27, 2010. A document published by US EPA subsequent to the 2010 SAP meeting states that "the Agency considered the atrazine-induced disruption of the LH surge, in rats, as the key event of the cascade of changes leading to the adverse reproductive outcomes following

[69] Title 27, Cal Code of Regs., section 25306(l)(4)
[70] Available at http://www.epa.gov/scipoly/sap/pubs/charter.pdf

atrazine exposure."[71] It is therefore apparent that, irrespective of any advice received from the SAP, US EPA identified atrazine (and the other five chemicals identified on the basis of the same mechanism of action) as causing reproductive toxicity.

3. *OEHHA did not exercise due diligence in evaluating the scientific record because it relied on statements made by the USEPA originating during or prior to 2006, whereas substantial new "scientifically valid data" were presented to the USEPA after 2006*.
   Response: OEHHA relied upon documents published by the authoritative body that formally identify the triazines as causing reproductive toxicity according to the criteria specified in regulations[72] (see response to comment 2.3). The commenter failed to identify any documents published subsequently by US EPA which repudiate that formal identification, nor has OEHHA been able to do so. Further, OEHHA has taken into account data not considered by US EPA, some of which was submitted by commenters and some of which was identified by OEHHA (see responses to comments 4.3 and 4.4 below). For the reasons given in those responses, OEHHA has determined that these new data do not "clearly establish that the chemical does not satisfy the criteria of [Section 25306] subsection (g), paragraph (1) or subsection (g), paragraph 2"[73].

4. *This new scientific data demonstrated that, based upon what is known about the indicators of reproductive or development effects in animals, and new information on pharmacokinetics, it is not biologically plausible that humans exposed to the chlorotriazines will display developmental or reproductive toxicity*.
   Response: The issues of biological plausibility and the studies cited by the commenter in support of this opinion are the same as those cited by other commenters who raised the same issues. Those issues are addressed in the responses to comments 3.4 and 3.13.

Nothing in Attachment K changes OEHHA's determination that US EPA's conclusions are supported by substantial evidence.

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[71] Re-Evaluation of Human Health Effects of Atrazine: Review of Cancer Epidemiology, Non-cancer Experimental Animal and *In vitro* Studies and Drinking Water Monitoring Frequency. Presented Jointly To The FIFRA Scientific Advisory Panel By: U.S. Environmental Protection Agency Office of Pesticide Programs Health Effects Division and Environmental Fate and Effects Division in collaboration with the Office of Research and Development. Presented On: July 26-29, 2011. (Page 16). Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2011-0399-0013

[72] Title 27, Cal Code of Regs., section 25306

[73] Title 27, Cal Code of Regs., section 25306(h)

Attachment L is a letter by Dr. James Lamb. The specific points raised by Dr. Lamb in his letter are addressed in the responses to comments 3.3 through 3.13 and 4.1, 4.3, and 4.4.

4.3 Comment:

Citing a study by Simpkins et al. (2011)[74] that was published subsequent to US EPA's consideration of the triazines, Lamb (p. 2-3) compared the estrous cycle in rats with the menstrual cycle in humans and commented that "Unlike the rat, the LH surge in humans appears to occur independently from a GnRH signal and is primarily the result of positive feedback from estradiol".

Same comment made by Syngenta (pp. 6-8) and in Sygenta Attachments A (p. 9) and B (p. 10).

Response:

The relationship between GnRH and the LH surge in humans has been discussed in the response to comment 3.6. As noted in that response, even if GnRH does not directly control the LH surge in humans, that does not demonstrate that a reduction in GnRH is not relevant to reproductive function, including the LH surge, in humans. OEHHA agrees that there are species differences in the control of ovulation between humans and rodents. However, as discussed in detail below, there is ample evidence that both GnRH and LH together with ovarian steroids play an important role in control of ovulation in primates, including humans. In the study cited by the commenter (Simpkins et al., 2011), the authors concluded that "it is plausible that high doses of atrazine could suppress the LH surge in women by interfering with GnRH pulse generation", a position consistent with both US EPA's and OEHHA's interpretation of the data. Thus, OEHHA continues to agree with US EPA that the mechanism of action of the triazines, affecting GnRH and LH, and the adverse effects on reproduction and development resulting from that mechanism of action, are relevant to humans.

Irrespective of species, one of the most critical steps in female mammalian reproduction is ovulation, in which gametes (eggs) are produced by the ovaries. Ovulation is finely controlled by several factors such as ovarian and hypothalamic hormones. The hypothalamus is a part of the brain that has control over several functions in the body; its function in the control of ovulation is mediated by the peptide gonadotropin-releasing hormone (GnRH)[75,76]. GnRH will interact with the pituitary gland to induce the liberation

[74] Simpkins, J. W., Swenberg, J. S., Weiss, N.,Brusick, D., Eldridge, J. C., Stevens, J. T., Handa, R. J., Hovey, R. C., Plant, T. M., Pastoor, T. P. and Breckenridge, C. B. 2011. Atrazine and breast cancer: A framework assessment of the toxicological and epidemiological evidence. Toxicol. Sci., 123:441-459.

[75] Filicori M, Flamigni C, Campaniello E, Ferrari P, Meriggiola MC, Michelacci L, Pareschi A and Valdiserri A (1989). Evidence for a specific role of GnRH pulse frequency in the control of the human menstrual cycle. *Am J Physiol* **257**(6 Pt 1): E930-936.

[76] Reame NE, Sauder SE, Case GD, Kelch RP and Marshall JC (1985). Pulsatile Gonadotropin Secretion in Women with Hypothalamic Amenorrhea: Evidence that Reduced Frequency of Gonadotropin-

of gonadotropins. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) are gonadotropins that act on the ovary to stimulate ovarian development (follicle growth), the production and release of ovarian hormones, and the liberation from a mature follicle of the female gamete (oocyte or egg) at the time of ovulation.

Evidence supporting active participation of the hypothalamus through GnRH on the control of ovulation in women and non-human primate models has been reviewed by Berga and Naftolin (2012)[77]. This review considers how internal and external factors interact with the neuroendocrine system to cause anovulation and amenorrhea in women. The document states that there are three main causes for these conditions: "(1) genetic diseases that interfere with the migration of GnRH cells into the brain or result in misfolding of GnRH; (2) input from the brain that interrupts normal feedback (e.g. stress and weight loss amenorrhea); and (3) the effect of agents which alter central neurotransmission and hypothalamic function". The reviewers concluded that "…all types of hypothalamic insufficiency result in insufficient stimulation of the ovaries". In addition it is stated that: "These data show that the previously held view that the hypothalamus is a passive participant in the normal cycle and the development of the preovulatory peak is incorrect."

In primates, the hypothalamus not only controls the LH surge but also follicle development. While a decreased secretion of GnRH at the midcycle may be a part of the normal hormone milieu for ovulation in women, a certain minimum level of GnRh is also necessary for follicle maturation (Martin et al., 1998)[78]. Follicle maturation is required for ovulation as the absence of mature follicles will reduce the amount of estradiol produce by that ovary. Martin et al. (1998) states that "these findings suggest that the relative amount of GnRH required for folliculogenesis and luteal-phase support is greater than that required to produce an LH surge". Estradiol has a double action in the feedback controlling gonadotropin secretion. One action regulates the number of GnRH receptors in the pituitary gland and the other suppresses the release of GnRh by the hypothalamus. In the non-human primate animal model, as the follicle matures, a large secretion of estradiol causes a decrease followed by an increase in GnRH secretion and upregulation of the GnRH receptors in the pituitary (Pau *et al*., 1993)[79] right at the time of the mid-cycle LH surge.

Releasing Hormone Secretion Is the Mechanism of Persistent Anovulation. *The Journal of Clinical Endocrinology & Metabolism* **61**(5): 851-858.

[77] Berga S and Naftolin F (2012). Neuroendocrine control of ovulation. Gynecol Endocrinol 28 Suppl 1: 9-13.

[78] Martin KA, Welt CK, Taylor AE, Smith JA, Crowley WF, Jr. and Hall JE (1998). Is GnRH reduced at the midcycle surge in the human? Evidence from a GnRH-deficient model. Neuroendocrinology 67(6): 363-369.

[79] Pau KY, Berria M, Hess DL and Spies HG (1993). Preovulatory gonadotropin-releasing hormone surge in ovarian-intact rhesus macaques. *Endocrinology* **133**(4): 1650-1656.

The reference cited by the commenter, Simpkins et al. (2011)[80], presents a review of publications related to the LH surge and its control by GnRH. The stated goal of this review is to present "…a case study utilizing the reviewing methodology described by Adami et al. (2011) wherein toxicological and epidemiological evidence were combined in a systematic framework to conclude whether a causal relationship exists between atrazine exposure and breast cancer in humans." In a section describing the HPG control axis and ovulation in women, Simpkins et al (2011)[81] cited three references (Hall et al., 1994, Martin et al., 1998, and Ottowitz et al., 2008) supporting the concept that GnRH may not increase during the midcycle LH surge in women. The data presented by Hall et al. (1994)[82] suggest that there is a decrease in GnRH at the midcycle LH surge in women. However, that study also presents data demonstrating that blocking GnRH with an antagonist reduces the amount of LH secreted at different times in the menstrual cycle. The data by Martin et al. (1998)[83], in addition to supporting the uncoupling between GnRH and LH at the mid cycle surge, also suggest that a certain minimum level of GnRH is necessary to maintain maturation of the follicle. The work by Ottowitz et al (2008)[84] presents a novel technique to detect metabolic changes in hypothalamic and pituitary cells in response to positive and negative feedback from estradiol by measuring serum LH and estradiol in postmenopausal women, but does not provide information relevant to the relationship between GnRH and the the LH surge in humans.

4.4 Comment:

To further support the argument that there are several significant differences in the induction of the LH surge between rats and humans, Lamb (p. 3) commented, that "The timing and control of ovulation in humans is not linked with a circadian signal and the primary site for feedback from estradiol is the pituitary, not the preoptic area of the hypothalamus which is the feedback site in rats (Plant et al. 2012)[85]." (Lamb, p. 3).

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[80] Simpkins, J. W., Swenberg, J. S., Weiss, N., Brusick, D., Eldridge, J. C., Stevens, J. T., Handa, R. J., Hovey, R. C., Plant, T. M., Pastoor, T. P. and Breckenridge, C. B. (2011). Atrazine and breast cancer: A framework assessment of the toxicological and epidemiological evidence. Toxicol. Sci., 123,441-459.

[81] id

[82] Hall JE, Taylor AE, Martin KA, Rivier J, Schoenfeld DA and Crowley WF (1994). Decreased release of gonadotropin-releasing hormone during the preovulatory midcycle luteinizing hormone surge in normal women. *Proceedings of the National Academy of Sciences* **91**(15): 6894-6898.

[83] Martin, K. A., C. K. Welt, A. E. Taylor, J. A. Smith, W. F. Crowley, Jr. and J. E. Hall (1998). "Is GnRH reduced at the midcycle surge in the human? Evidence from a GnRH-deficient model". Neuroendocrinology **67**(6): 363-9.

[84] Ottowitz, W. E., D. D. Dougherty, A. J. Fischman and J. E. Hall (2008). "[18F]2-fluoro-2-deoxy-D-glucose positron emission tomography demonstration of estrogen negative and positive feedback on luteinizing hormone secretion in women". J Clin Endocrinol Metab **93**(8): 3208-14.

[85] Plant, T. M. (2012). A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory LH surge in the human, Old World monkey and rodent. Front. Neuroendocrinol.,33,160-168.

Response:

Ovulation is not only controlled by internal factors but also by external ones (Berga and Naftolin, 2012)[86]. It is recognized that some laboratory animals respond to circadian rhythms such as light (e.g., rats and mice), while others ovulate as a reflex action after mating (e.g., rabbits and cats). Ovulation in humans is controlled primarily by factors produced by the endocrine and nervous systems and, to a lesser extent, by environmental factors such as light and stress (Berga and Naftolin, 2012[87]; Kriegsfeld, 2013[88]).

OEHHA therefore agrees that ovulation in primates may not be linked to circadian rhythm in the same way as it is in the rodent animal model. However, there is evidence that the menstrual cycle of women is influenced by environmental factors, including circadian rhythm (i.e., time of day), indicating that the evidence of adverse reproductive effects in rodents is relevant to humans. For example, the preovulatory LH surge in humans, as in rats, is influenced by the time of day. In humans the surge occurs in the morning; in the rat it occurs in the evening (Kerdelhue et al., 2002)[89]. Physiologic clinical cases in which reproduction is affected such as athletic amenorrhea, hypothalamic amenorrhea, and other cases of stress-induced anovulation in women are some examples of how the environment and other factors play a role controlling the menstrual cycle and ovulation in women. In a recent review of the action of the neuropeptide kisspeptin on the control of ovulation in mammals, the author wrote: "Across species, including humans, disruptions to circadian timing result in pronounced deficits in ovulation and fecundity" (Kriegsfeld, 2013)[90].

Further evidence of the role of the environment in ovarian activity is from patients with idiopathic amenorrhea, where behavioral therapy may be able to restore ovarian activity (Berga *et al.*, 2003)[91]. These studies show that emotional factors (sometimes controlled by the social environment of the patient) influence normal ovarian activity. Further, several authors reported that ovarian activity may be controlled by cortisol (a stress

[86] Berga S and Naftolin F (2012). Neuroendocrine control of ovulation. Gynecol Endocrinol 28 Suppl 1: 9-13.
[87] id
[88] Kriegsfeld L (2013). Circadian Regulation of Kisspeptin in Female Reproductive Functioning. In: Kisspeptin Signaling in Reproductive Biology. Kauffman, AS and Smith, JT: Springer New York, pp. 385-410
[89] Kerdelhue B, Brown S, Lenoir V, Queenan JT, Jr., Jones GS, Scholler R and Jones HW, Jr. (2002). Timing of initiation of the preovulatory luteinizing hormone surge and its relationship with the circadian cortisol rhythm in the human. *Neuroendocrinology* **75**(3): 158-163.
[90] Kriegsfeld L (2013). Circadian Regulation of Kisspeptin in Female Reproductive Functioning. In: Kisspeptin Signaling in Reproductive Biology. Kauffman, AS and Smith, JT: Springer New York, pp. 385-410.
[91] Berga SL, Marcus MD, Loucks TL, Hlastala S, Ringham R and Krohn MA (2003). Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy. Fertil Steril 80(4): 976-981.

hormone) (Brundu *et al.*, 2006[92]; Williams *et al.*, 2007[93]; Vulliemoz *et al.*, 2008[94]; Ahn *et al.*, 2011[95], as reviewed by Williams and Kriegsfeld, 2012[96]). This indicates that the environment plays a role in normal physiology influencing the HPO axis activity and therefore the reproductive cycle in women.

OEHHA agrees that in humans, the primary site for feedback from estradiol is the pituitary. OEHHA also agrees that the hypothalamic site for GnRH control is the preoptic area in rodents, while in primates, including humans, it is the bilateral arcuate nuclei in the mid hypothalamus (Berga and Naftolin, 2012)[97]. However, as discussed above and in the response to comment 4.3, these differences do not demonstrate that adverse effects on ovulation from exposure to triazines are not biologically plausible in humans.

Thus, nothing in these studies changes OEHHA's determination that US EPA's conclusions are supported by substantial evidence.

[92] Brundu B, Loucks TL, Adler LJ, Cameron JL and Berga SL (2006). Increased cortisol in the cerebrospinal fluid of women with functional hypothalamic amenorrhea. J Clin Endocrinol Metab 91(4): 1561-1565.
[93] Williams NI, Berga SL and Cameron JL (2007). Synergism between psychosocial and metabolic stressors: impact on reproductive function in cynomolgus monkeys. Am J Physiol Endocrinol Metab 293(1): E270-276.
[94] Vulliemoz NR, Xiao E, Xia-Zhang L, Rivier J and Ferin M (2008). Astressin B, a nonselective corticotropin-releasing hormone receptor antagonist, prevents the inhibitory effect of ghrelin on luteinizing hormone pulse frequency in the ovariectomized rhesus monkey. Endocrinology 149(3): 869-874.
[95] Ahn RS, Choi JH, Choi BC, Kim JH, Lee SH and Sung SS (2011). Cortisol, estradiol-17beta, and progesterone secretion within the first hour after awakening in women with regular menstrual cycles. J Endocrinol 211(3): 285-295.
[96] Williams WP, 3rd and Kriegsfeld LJ (2012). Circadian control of neuroendocrine circuits regulating female reproductive function. Front Endocrinol (Lausanne) 3: 60.
[97] Berga S and Naftolin F (2012). Neuroendocrine control of ovulation. Gynecol Endocrinol 28 Suppl 1: 9-13.